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(54) **Use of anthelmintic compositions for treating Anoplocephala perfoliata infections in equidae**
Verwendung von antihelminthischen Zusammensetzungen zur Behandlung der durch Anoplocephala perfoliata verursachten Infektionen bei Pferden
Utilisations des compositions antihelminthiques pour le traitement des infections dues au Anoplocephala perfoliata chez les équidés

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(56) References cited:
EP-A- 0 059 074 WO-A-95/05181
DE-A- 3 619 030 GB-A- 2 252 730
ZA-A- 8 402 571

- French and Chapman, The compendium, May 1992, 14(5), pp.655-663 "Tapeworms of the equine gastrointestinal tract"
- Duncan, Equine Vet. J., 1985, 17(2), pp.79-82, "Internal parasites of the horses and their control"

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Description

- [0001] The present invention relates to the use of a composition for the control and the treatment of parasitic infestations in Equidae and, in particular, for simultaneous control and treatment of infestations by *Anoplocephala perfoliata* in such animals.
- [0002] Avermectins and milbemycins are currently used in the treatment and control of roundworms and bots in horses and ponies. However, these compounds are known to be inactive against tapeworms. The widespread use of the anthelmintic ivermectin has recently been linked to a rise in the prevalence of the equine tapeworm *Anoplocephala perfoliata*.
- [0003] *Anoplocephala perfoliata* is found mainly in the caecum but tends also to cluster in the ileum near the ileocecal valve where it is associated with ulceration and reactive inflammation of the ileal wall. This clustering results in ulceration of the mucous membrane and inflammation with thickening and induration of the deeper layers of the intestinal wall. These pathological changes probably account for some cases of persistent diarrhoea and may predispose to intussusception of the ileum into the caecum or rupture of the bowel wall in the vicinity of the ileocecal valve.
- [0004] It is therefore highly desirable to have a composition which has activity against both cestode and nematode infestations in Equidae and more particularly in horses.
- [0005] The invention relates to the use of an anthelmintic composition comprising an amount of praziquantel suitable for administering to equine animals a dose of 0.5 to 2.0 mg of praziquantel per kg of animal body weight, together with an effective amount of one anthelmintic agent selected from avermectins or milbemycins or derivatives thereof for the preparation of a medicament for orally controlling and treating infestations by *Anoplocephala perfoliata* in equine animals.
- [0006] Indeed, trials have shown that, when praziquantel is orally administered to horses in combination with an avermectin or a milbemycin or a derivative thereof, a surprising increase of the anthelmintic spectrum is obtained due to the administration in combination. Furthermore a synergistic effect is observed to the extent that when in combination with avermectins or milbemycins the required dosage rate for praziquantel in equine animals is between 0.5 and 2.0 mg per kg of animal body weight. This synergistic activity is even higher with a paste formula.
- [0007] In one preferred embodiment, the anthelmintic agent is an avermectin.
- [0008] Advantageously, said avermectin is abamectin.
- [0009] In another preferred embodiment, the anthelmintic agent is ivermectin.
- [0010] In yet another preferred embodiment, the anthelmintic agent is moxidectin.
- [0011] Whatever the embodiment, the composition comprises an amount of praziquantel suitable for administering to equine animals a dose of 0.5 to 2.0 mg of praziquantel per kg of animal body weight.
- [0012] Advantageously, when the anthelmintic agent is abamectin or ivermectin, the composition comprises abamectin or ivermectin suitable for administering to equine animals doses of about 0.2 mg of abamectin or ivermectin per kg of animal body weight.
- [0013] Preferably, the composition is in the form of a paste.
- [0014] Anthelmintic formulations containing praziquantel together with another anthelmintic such as for example levamisole, albendazole, oxfendazole, moxidectin, ivermectin, have been disclosed in the British Patent Application 2 252 730 of Ancare Distributors Limited. However, the various associations disclosed in this Patent Application are not synergistic and only increase the anthelmintic spectrum in sheep. According to Ancare Distributors Limited, the recommended dose rate of praziquantel in such associations is between 2.0 and 7.5 mg per kg of animal body weight.
- [0015] According to the present invention, it has been discovered that the association between praziquantel and an avermectin or a milbemycin or a derivative thereof shows a surprising synergy in the treatment of horse tapeworms. It allowed the use of praziquantel against *Anoplocephala perfoliata* in Equidae at a dose rate between 0.5 and 2.0 mg per kg of animal body weight. These dosages are significantly lower than in the already described formulations.
- [0016] Campbell et al. in the South African Patent Application 842571 disclose compositions containing avermectin compounds with one compound selected from various anthelmintic agents, and having some synergetic effects in the treatment of parasitic diseases. One of these anthelmintic compounds is praziquantel.
- [0017] However, Campbell et al. do not contemplate the possibility of using the compositions described therein for the treatment of infestations by *Anoplocephala perfoliata* in horses. Furthermore, when the avermectin compound is associated with praziquantel, the latter is administered at a dosage rate from 5 to 50 mg/kg of body weight.
- [0018] Kitano in the European Patent Application 0 059 074 also discloses associations of macrolide anthelmintic agents (avermectins) and a variety of several anthelmintic agents like benzimidazole, salicylamide and isoquinoline compounds with enhanced anthelmintic activity. However, Kitano studies on cestodes did not show any evident synergy of any association on *Anoplocephala perfoliata*.
- [0019] According to the present invention, the activity of praziquantel against *Anoplocephala perfoliata* is increased in association with an avermectin or a milbemycin compound or a derivative thereof.
- [0020] Moreover, the association exhibits higher synergistic activity as a paste formula which allowed a better bio-

disponibility of praziquantel in horses.

[0021] Praziquantel (2(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one) is a relatively insoluble material in water and consequently the applicant has devised formulations for administration of the compound subject of this invention in the form of paste, drench, tablet or pellet.

Examples of formulations in accordance with the present invention will be described hereafter without limiting the generality of the invention as above described.

[0023] The range of active percentages of a typical formula in accordance with this invention could be as indicated thereafter:

Praziquantel and Ivermectin or Abamectin or Moxidectin or Doramectin	0.1-30% w/v 0.05-5% w/v 0.05-5% w/v 0.05-5% w/v 0.05-5% w/v
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and one or more of the following ingredients to enhance stability and/or other characteristics of the composition : surfactants, preservatives, viscosity agents, stabilisers, flavours and colours.

[0024] Ivermectin is a semisynthetic derivative of avermectins. Ivermectin contains at least 80% of 22,23-dihydroavermectin B1a and less than 20% of 22,23-dihydroavermectin B1b. Ivermectin is disclosed in Australian Patent 519569.

[0025] Abamectin or avermectin B1 contains at least 80% of avermectin B1a and not more than 20% of avermectin B1b. Abamectin is disclosed in Australian Patent 513641.

[0026] Moxidectin [spiro (11,5-methano-2Hm13G, 17H-furo(4,3,2-pg) (2,6) benzodioxacyclo octadectin-13,2'-(2H) pyran-7-one,20,20b-dihydroxy-6'-(1,3-dimethyl-T-butenyl)= 4'-(methoxymino)-3'-4',5',6,6',7,10,11,14,15,17a,20,20a, 20b-tetradecahydro-5'6,8,19-teramethyl-(6R-(2aZ,4E,5'S*, 6R*(E),8E,11R*,13S*,15R*,17aR*,20R*,20bS*))] is a new broad spectrum endectocide.

[0027] Doramectin (25-cyclohexyl-5-O-demethyl-25-de-1(methylpropyl)avermectin A1a is an avermectin.

[0028] According to the invention, when praziquantel is orally administered in combination with an avermectin, a milbemycin or a derivative thereof, the dosage rate of praziquantel required for efficiently treating equine animals against nematodes and more particularly against *Anoplocephala perfoliata* is between 0.5 and 2.0 mg per kg of animal body weight. However, it has been observed that praziquantel may be administered in higher dosage rates without adverse effects and in this regard dosage rates of up to 7.5 mg per kg of body weight have been tested.

EXAMPLE 1 : ABAMECTIN-PRAZIQUANTEL PASTE FOR HORSES

[0029]

ABAMECTIN (AVERMECTIN B1)	0,4 g
PRAZIQUANTEL	50 g
DIETHYLENE GLYCOL PALMITO STEARATE	80 g
SODIUM METABISULFITE	1 g
SORBITOL SOLUTION (NON-CRYSTALLISING)	120 g
GLYCEROL FORMAL	60 ml
POLYETHYLENE GLYCOL 400	60 ml
METHYL HYDROXYBENZOATE	0,5 g
PROPYL HYDROXYBENZOATE	0,05 g
BENZYL ALCOHOL	10 g
OAT MEAL FLOUR	300 g
PURIFIED WATER	q.s. to 1 litre

[0030] The manufacture of the formulations of Example 1 is in accordance with the following procedures :

EFFICACY OF THE FORMULATION OF EXAMPLES 1, 2, 3, 4 AND 5 AGAINST NEMATODES, ARTHROPOD PARASITES AND CESTODES IN HORSES IN A CRITICAL TRIAL

Anthelmintic	Dosage mg/kg	% Efficacy Strongylidae	% Efficacy <i>Gasterophilus</i> spp.	% Efficacy <i>Parascaris equorum</i>	% Efficacy <i>Anoplocephala perfoliata</i>
Abamectin	0.2	100	100	100	0
Praziquantel	0.1	0	0	0	0
Praziquantel	0.5	0	0	0	27
Praziquantel	1	0	0	0	58
Praziquantel	2	0	0	0	71
Praziquantel	5	0	0	0	83
Abamectin	0.2	100	100	100	39
Praziquantel	0.1				
Abamectin	0.2	100	100	100	89
Praziquantel	0.5				
Abamectin	0.2	100	100	100	100
Praziquantel	1				
Abamectin	0.2	100	100	100	100
Praziquantel	2				
Abamectin	0.2	100	100	100	100
Praziquantel	5				

EXAMPLE 11 : TRIAL 2

[0049] A trial involving Ivermectin drench (1 ml per 10 kg of body weight equivalent to 0.2 mg of Ivermectin per kg B.W.), praziquantel drench (0.5 to 2 mg of praziquantel per kg of body weight), and formulations in accordance with Examples 6, 7 and 8.

[0050] Seven groups of 6 horses per group were involved in the study. Area of origin of the horses was well known for having internal parasitism problem and specifically tapeworms (*Anoplocephala perfoliata*) infestation.

[0051] A high level of efficacy was demonstrated by the combination formula of Examples 7 and 8 against roundworms, arthropod parasites and tapeworms.

[0052] Synergistic activity of praziquantel and ivermectin shows 100 % removal of *Anoplocephala perfoliata* with 0.2 mg of ivermectin per kg B.W. and 2 mg of praziquantel per kg B.W.

EFFICACY OF THE FORMULATION OF EXAMPLES 6, 7 AND 8 AGAINST NEMATODES, ARTHROPOD PARASITES AND CESTODES IN HORSES IN A CRITICAL TRIAL

Anthelmintic	Dosage mg/kg	% Efficacy Strongylidae	% Efficacy <i>Gasterophilus</i> spp.	% Efficacy <i>Parascaris aquorum</i>	% Efficacy <i>Anoplocephala perfoliata</i>
Ivermectin	0.2	100	100	100	0
Praziquantel	0.5	0	0	0	21
Praziquantel	1	0	0	0	43
Praziquantel	2	0	0	0	59
Ivermectin	0.2	100	100	100	68
Praziquantel	0.5				
Ivermectin	0.2	100	100	100	91
Praziquantel	1				

(continued)

EFFICACY OF THE FORMULATION OF EXAMPLES 6, 7 AND 8 AGAINST NEMATODES, ARTHROPOD PARASITES AND CESTODES IN HORSES IN A CRITICAL TRIAL					
Anthelmintic	Dosage mg/kg	% Efficacy Strongylidae	% Efficacy <i>Gasterophilus spp.</i>	% Efficacy <i>Parascaris aquorum</i>	% Efficacy <i>Anoplocephala perfoliata</i>
Ivermectin	0.2	100	100	100	
Praziquantel	2				100

Claims

1. Use of an anthelmintic composition comprising an amount of praziquantel suitable for administering to equine animals a dose of 0.5 to 2.0 mg of praziquantel per kg of animal body weight, together with an effective amount of an anthelmintic agent selected from avermectins or milbemycins or derivatives thereof for the preparation of a medicament for orally controlling and treating infestations by *Anoplocephala perfoliata* in equine animals.
2. Use of an anthelmintic composition according to claim 1, wherein the anthelmintic agent is abamectin.
3. Use of an anthelmintic composition according to claim 1, wherein the anthelmintic agent is ivermectin.
4. Use of an anthelmintic composition according to claim 1, wherein the anthelmintic agent is moxidectin.
5. Use of an anthelmintic composition according to claim 2, which comprises an amount of abamectin suitable for administering to equine animals about 0.2 mg of abamectin per kg of animal body weight.
6. Use of an anthelmintic composition according to claim 3, which comprises an amount of ivermectin suitable for administering to equine animals about 0.2 mg of ivermectin per kg of animal body weight.
7. Use of an anthelmintic composition according to anyone of preceding claims, which is in the form of a paste.

Patentansprüche

1. Verwendung einer anthelminthischen Zusammensetzung umfassend eine Praziquantel-Menge, die geeignet ist, um Pferden eine Dosis von 0,5 bis 2,0 mg Praziquantel pro kg Körpergewicht des Tieres zu verabreichen, zusammen mit einer wirksamen Menge eines Anthelminthikums, ausgewählt aus Avermectinen oder Milbemycinen oder Derivaten davon, zur Herstellung eines Medikaments zur oralen Kontrolle und Behandlung von Befall durch *Anoplocephala perfoliata* in Pferden.
2. Verwendung einer anthelminthischen Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß das Anthelminthikum Abamectin ist.
3. Verwendung einer anthelminthischen Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß Anthelminthikum Ivermectin ist.
4. Verwendung einer anthelminthischen Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß Anthelminthikum Moxidectin ist.
5. Verwendung einer anthelminthischen Zusammensetzung nach Anspruch 2, umfassend eine Abamectin-Menge, die geeignet ist, Pferden etwa 0,2 mg Abamectin pro kg Körpergewicht des Tieres zu verabreichen.
6. Verwendung einer anthelminthischen Zusammensetzung nach Anspruch 3, umfassend eine Ivermectin-Menge, die geeignet ist, Pferden etwa 0,2 mg Ivermectin pro kg Körpergewicht des Tieres zu verabreichen.
7. Verwendung einer anthelminthischen Zusammensetzung nach einem der vorhergehenden Ansprüche, dadurch

gekennzeichnet, daß sie in Form einer Paste vorliegt.

Revendications

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1. Utilisation d'une composition anthelminthique comprenant une quantité de praziquantel convenable pour administrer à des équidés une dose de 0,5 à 2,0 mg de praziquantel par kg de poids corporel de l'animal, ainsi qu'une quantité efficace d'un agent anthelminthique choisi parmi des avermectines ou des milbémécines ou leurs dérivés, pour la préparation d'un médicament destiné au contrôle et au traitement par voie orale des infestations par *Anoplocephala perfoliata* chez des équidés.
2. Utilisation d'une composition anthelminthique suivant la revendication 1, dans laquelle l'agent anthelminthique est l'abamectine.
3. Utilisation d'une composition anthelminthique suivant la revendication 1, dans laquelle l'agent anthelminthique est l'ivermectine.
4. Utilisation d'une composition anthelminthique suivant la revendication 1, dans laquelle l'agent anthelminthique est la moxidectine.
5. Utilisation d'une composition anthelminthique suivant la revendication 2, qui comprend une quantité d'abamectine convenable pour administrer à des équidés environ 0,2 mg d'abamectine par kg de poids corporel de l'animal.
6. Utilisation d'une composition anthelminthique suivant la revendication 3, qui comprend une quantité d'ivermectine convenable pour administrer à des équidés environ 0,2 mg d'ivermectine par kg de poids corporel de l'animal.
7. Utilisation d'une composition anthelminthique suivant l'une quelconque des revendications précédentes, qui est sous la forme d'une pâte.